

Systematic review and cost-effectiveness of pharmacokinetically guided sunitinib individualized treatment for patients with metastatic renal cell carcinoma

Tingting Chen*, Jiahe Chen*, Chaoxin Chen, Jianming Guo, Xin He, Song Zheng, Maobai Liu and Bin Zheng

Ther Adv Med Oncol

2022, Vol. 14: 1–13

DOI: 10.1177/
17588359221085212

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Abstract

Background: Sunitinib has a narrow therapeutic window, with considerable differences between patients. Dosing based on pharmacokinetics (PK) may help overcome some of those issues. This study aims to evaluate and compare the cost-effectiveness of PK-guided individualized treatment of sunitinib with its standard dose in patients with metastatic renal cell carcinoma (mRCC).

Methods: A comprehensive literature search was performed, and relevant values were used to provide information for the decision analysis model. Utility data were derived from published studies, and costs were obtained from the perspective of payers in China and the United States. A Markov model was established to evaluate the associated costs and health outcomes for patients. The primary outputs of the model included lifetime costs, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratio (ICER). One-way and probability sensitivity analyses were conducted to evaluate the potential uncertainties of parameters.

Results: Cost-effective analysis showed that the QALY of the PK-guided group increased by 0.83 compared with that in the standard dose group. From the perspective of both countries' health systems, the cost of PK-guided dose was lower than that of standard dose. Hence, PK-guided treatment was the dominant strategy. One-way and probability sensitivity analyses confirmed the reliability of these results.

Conclusion: On the basis of currently available data, PK-guided sunitinib treatment may be a safe, effective, and economical intervention for patients with mRCC.

Keywords: cost-effectiveness, metastatic renal cell carcinoma, pharmacokinetic guidance, standard dose, sunitinib

Received: 8 October 2021; revised manuscript accepted: 15 February 2022.

Introduction

Sunitinib is an oral multi-target tyrosine kinase inhibitor acting on signaling cascades involved in proliferation and tumor progression. This drug has been approved by the Food and Drug Administration as a first-line treatment for advanced and/or metastatic renal cell carcinoma (mRCC)¹ and a second-line treatment in locally advanced inoperable and metastatic gastrointestinal stromal tumors.² The recommended starting

dose and schedule for sunitinib is 50 mg/day for 28 days, followed by a 14-day break. At this daily dose of sunitinib, the target total trough concentration (TTL, sum of trough concentrations of sunitinib and its metabolites) that the patient should achieve is 50–100 ng/ml.^{3,4} Owing to the large individual patient variability, drug levels may exceed this range, with severe toxicity such as thrombocytopenia, anorexia, fatigue, hand-foot syndrome, and bleeding events. Sunitinib

Correspondence to:

Maobai Liu
Fujian Medical University
Union Hospital, 29, Xinquan
Road, Gulou District,
Fuzhou City 350001, Fujian
Province, China
liumaobai@163.com

Bin Zheng
Department of Pharmacy,
Fujian Medical University
Union Hospital, Fuzhou
350001, Fujian, China
College of Pharmacy,
Fujian Medical University,
Fuzhou, China
zhengb5@fjmu.edu.cn

Tingting Chen
Chaoxin Chen
Jianming Guo
Xin He
College of Pharmacy,
Fujian Medical University,
Fuzhou, China

Department of Pharmacy,
Fujian Medical University
Union Hospital, Fuzhou,
China

Jiahe Chen
Department of
Pharmaceutical and
Health Economics, School
of Pharmacy, University of
Southern California, Los
Angeles, CA, USA

Leonard D. Schaeffer
Center for Health Policy &
Economics, University of
Southern California, Los
Angeles, CA, USA

Song Zheng
Department of Urology,
Fujian Medical University
Union Hospital, Fuzhou,
China

*These authors have
contributed equally to
this work and share first
authorship.



could also induce rare but potentially life-threatening events such as intestinal perforation and interstitial lung disease.^{1,5} Given that these toxicities are difficult to treat and predict, doctors must closely monitor all patients who have started sunitinib treatment. Individual differences in patients will lead to high systemic exposure to sunitinib and its active metabolite concentrations for some patients, resulting in differences in toxicity. In this context, predictive indicators must be identified for the prevention of severe toxicity caused by sunitinib. High sunitinib blood levels are associated with longer progression-free survival (PFS), overall survival (OS), and other curative effects.⁶ However, the therapeutic index of this drug is narrow, and its systemic exposure varies greatly among patients. Pharmacokinetics (PK)-guided dosing has been proposed as a strategy to regulate sunitinib medication⁷ and obtain optimal dose adjustment, thereby improving drug efficacy and avoiding adverse side effects.

Although therapeutic drug monitoring (TDM) has long been implemented for aminoglycosides, vancomycin, and antiepileptics and has been proven as cost-effective,⁸ this strategy is not widely applied for sunitinib. To date, only five studies have reported the clinical efficacy and safety of PK-guided sunitinib dosing,^{9–13} and no cost-effectiveness analysis has been conducted. On one hand, PK guidance can improve dose management, reduce costs, and enhanced treatment outcomes. On the other hand, this strategy also increases the cost of patient care, and its economic remains unclear. Here, an inductive analysis of existing clinical research and a cost-effectiveness analysis on PK-guided sunitinib treatment were conducted to provide patients with economical and effective treatment strategies.

Methods

Systematic review

Search strategy. In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (Supplementary Tables S3), a comprehensive search was conducted on PubMed, Embase and Cochrane Library, CNKI, Wanfang Database, and VIP Database to identify eligible papers published up to January 2021. The search terms were as follows: sunitinib, pharmacokinetics, PK, TDM, therapeutic drug monitoring, individualized dose adjustment, patient

specificity, and individualized. Subject and free terms were used. The search strategy was detailed in Supplementary Tables S1. The reference lists of retrieved articles and related reviews were also examined manually for additional studies. Inclusion criteria were as follows: (1) human subject research; (2) randomized controlled trials (RCTs) or cohort studies; (3) sunitinib dosage was adjusted *via* PK tools (PK equations or software) in the intervention group; (4) sunitinib was taken as standard dosing without the aid of PK tools in the control group; and (5) in the case of pooled articles based on similar patients, only the high-quality or the most recent study was selected. Exclusion criteria were as follows: (1) outcome indicators did not include PFS, OS, or toxicity; (2) study subjects were not patients with advanced/mRCC; (3) insufficient clinical data – for example, data were reported as a conference abstract, or the detailed dosing method was not provided; and (4) publications were not written in Chinese or English.

Quality assessment and data abstraction. Quality assessment and data extraction were independently performed by two of the authors, and disagreements were resolved through discussion or consultation with the third author. Cochrane risk of bias criteria was used to assess the potential risk of bias in RCTs.¹⁴ For cohort studies, quality was assessed using the Newcastle–Ottawa Scale (NOS): a study can be rated up to nine stars, and a final score of six stars or more is considered as high quality.¹⁵ Collected information included author name, publication year, country of origin, study design, disease type, tumor response and adverse events (AEs) evaluation criteria, treatment group, number of people, treatment regimens, and outcome indicators (including OS, PFS, and toxicity).

Cost-effectiveness analysis

Model design. A Markov model was constructed to evaluate the costs and health outcomes of mRCC treatment with sunitinib standard dose or PK-guided dose. The model included three health states reflecting different characteristics of the disease: PFS, progressed disease (PD), and death (Figure 1). PD status was treated by second-line treatment and third-line treatment depending on treatment. Patients in PFS could transit to second-line treatment or death after the initial treatment, those in the second-line treatment phase might continue to receive third-line treatment or

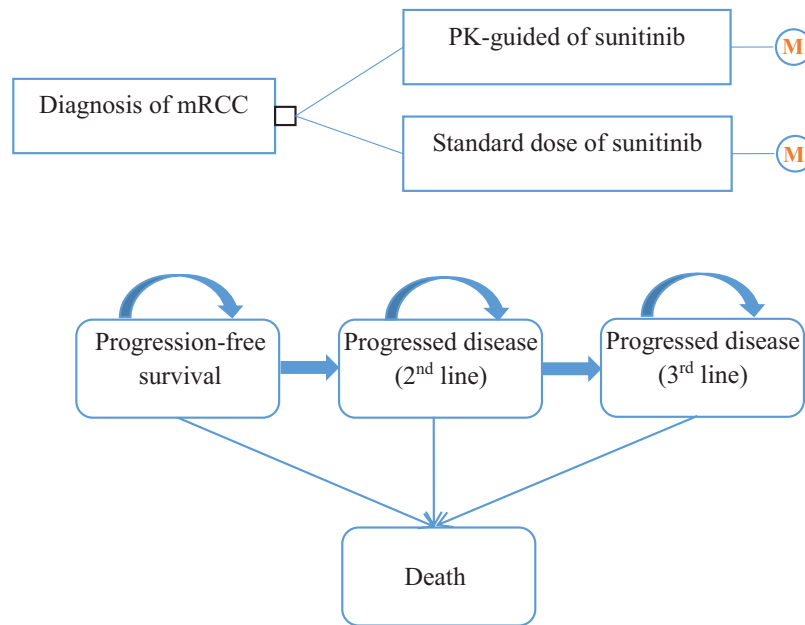


Figure 1. Markov model.

entered a state of death, and those in the third-line treatment might only deteriorate to death. Another possibility is to remain in the same condition after a cycle. Irrespective of salvage therapy effectiveness, patients could not return to the former state once the disease has progressed. According to the actual data on clinical sunitinib treatment, patients generally receive continuous treatment for 4 weeks, and medication is stopped for 2 weeks. Hence, the cycle length was set to 6 weeks in this work. The time horizon was 10 years because the survival rate of kidney cancer patients after 5 years was lower than 10%.¹⁶

TreeAge (TreeAge Software Inc, Williamstown, MA, USA) was used to program and analyze the model. The primary outputs of the model included total cost, QALY, and ICER. All costs and health output were discounted at a rate of 5%. Willingness to pay (WTP) threshold was set as US\$100,000 in the United States and US\$31,500 in China (3× the per capita gross domestic product of China in 2020).¹⁷ This study was performed in accordance with the recommendations of the Consolidated Health Economic Evaluation Reporting Standards checklist; details are presented in Supplementary Table S4.

Transition probabilities. The probabilities of transition from PFS to PD and from PD to death in the PK-guided group were obtained by fitting the PFS and OS curves in the phase II clinical trial.⁹

The probability of the standard dose group was derived from another phase II clinical trial of patients with similar eligibility criteria by using the curve data for the standard dose.¹⁸ PFS and OS Kaplan–Meier curves were digitized using GetData (version 2.26). An algorithm was applied to generate pseudo-individual patient data, and five survival distributions (Weibull, Log-logistic, Log-normal, Gompertz, and Exponential) were used to parameterize the model using the R software (Version 4.1.1). On the basis of Akaike information criterion (AIC), Bayesian information criterion (BIC), and clinical plausibility, Log-normal was chosen as the optimal fit for OS and PFS curve. The specific OS and PFS parameters are shown in Table 1. Survival probability was

calculated at time t : $S(t) = 1 - \varphi\left(\frac{\text{Log}(t) - \lambda}{\gamma^{-1}}\right)$,

(λ and γ are the scale parameters and shape parameters). Grade 3/4 AEs, such as fatigue, diarrhea, hypertension, thrombocytopenia, hand–foot syndrome, were included. Ratio parameters were derived from clinical trial data.^{9,18}

Cost and utility estimates. Cost estimation from the perspective of China and US health systems only considered direct medical costs, including the costs of sunitinib’s drug treatment, TDM, second-line treatment, third-line treatment, management of treatment-related grade 3/4 AEs, best supportive care (BSC), and terminal care^{19–25} as

Table 1. Key clinical data in the model.

Variables	Baseline value (range)	
	PK-guided	Standard dose
PFS	Scale = 2.5998; Shape = 0.9564; $r^2 = 0.9898^9$	Scale = 2.1714; Shape = 0.8085; $r^2 = 0.9908^{18}$
OS	Scale = 3.5995; Shape = 0.6925; $r^2 = 0.9859^9$	Scale = 3.1127; Shape = 0.8291; $r^2 = 0.9905^{18}$
Probability of third-line treatment	0.1880 (0.1504–0.2256) ⁹	
Probability of total AEs (grades 1 and 2)	0.1917 (0.15336–0.23004) ⁹	0.3453 (0.27624–0.41436) ¹⁸
AEs (grade ≥ 3) incidence		
Fatigue	0.0926 (0.07408–0.11112) ⁹	0.1795 (0.1436–0.2154) ¹⁸
Diarrhea	0.0277 (0.02216–0.03324) ⁹	0.0855 (0.0684–0.1026) ¹⁸
Hypertension	0.2820 (0.2256–0.3384) ⁹	0.2740 (0.2192–0.3288) ¹⁸
Thrombocytopenia	0.0370 (0.0296–0.0444) ⁹	0.1453 (0.11624–0.17436) ¹⁸
Hand foot syndrome	0.0513 (0.04104–0.06156) ⁹	0.1111 (0.08888–0.13332) ¹⁸
Probability of total AEs (grade ≥ 3)	0.0981 (0.07848–0.11772) ^a	0.1591 (0.12728–0.19092) ^a

AEs, adverse events; OS, overall survival; PFS, progression free survival; PK, pharmacokinetics.
^aProbability of total AEs is a weighted average of the five adverse events.

shown in Table 2. According to clinical trial data, the standard prescribed dose of sunitinib is 50 mg/day for 4 weeks, followed by 2 weeks of discontinuation. The PK-guided individual dose will either be increased or decreased depending on the TTL of sunitinib and its metabolites (SU012662). Given the lack of data on the actual dose intensity of PK-guided sunitinib, the drug cost of PK-guided group was assumed to be basically the same as that of standard group. Drug prices were acquired from Yaozhi.com in China and Red Book Wholesale Acquisition Cost in the United States. On the basis of data on actual clinical drug regimen and relevant literature, the patients' choice of second-line treatment included axitinib, pazopanib, nivolumab, and everolimus. Sorafenib was assumed as the third-line treatment. The proportion of each second- and third-line treatment was allocated according to the clinical data from RCTs.⁹ Patients received BSC after the failure of third-line therapy and treated with terminal care prior to death. The cost of AEs was based on the incidence of grade ≥ 3 AEs in clinical trials and the treatment cost of each AE and calculated as a weighted average. All costs of China health system were converted at the average exchange rate

of US dollars in 2020 (1 USD = 6.901 RMB) and discounted until 2020.

Life years were adjusted to health-related QALYs by using the utility value in the range of 0–1 (1 means complete health, 0 means death, QALY = health status utility value \times life years). Health utility values for PFS, second-line treatment, and third-line treatment were derived from literature,^{26,27} and disutility due to AEs was included in the model to account for the effect of AEs on the quality of life.²⁴

Sensitivity analysis. One-way sensitivity analysis was performed to examine the individual uncertainty of each parameter range, and the results were presented using a tornado diagram. The ranges of the parameters used in the one-way sensitivity analyses were obtained from literature; $\pm 20\%$ of the base-case value was used when data are not available. An assumed 50% discount of the price of sunitinib and related drugs for second-line therapy was used for one-way sensitivity analyses. For probabilistic sensitivity analysis, the Monte Carlo method was applied to simulate all variables with uncertainties within 95% CI for

Table 2. Cost estimates value and health preference data.

Parameters	Value (range)		Distribution
	China	United States	
Cost (\$)			
Cost of sunitinib/cycle	2515.58 (1257.79–5031.16) ¹⁹	19,701.85 (9850.93–39,403.70) ²²	Gamma
Cost of TDM	60 (48–72) ^a	80 (64–96) ²³	Gamma
Cost of second-line treatment/cycle	3794.6 (1897.3–7589.2) ¹⁹	19,437.7 (9718.85–38,875.4) ²²	Gamma
Cost of third-line treatment/cycle	555 (277–832.5) ¹⁹	11,190.48 (5595.24–16,785.72) ²²	Gamma
Cost of BSC/cycle	323 (258.4–387.6) ²⁰	1404.20 (1123.36–1685.04) ²⁴	Gamma
Cost of terminal care/patient	1940 (1552–2328) ²⁰	12,401.64 (9921.31–14,881.97) ²⁴	Gamma
Cost of managing AEs (grade \geq 3) per event			
Fatigue	107.66 (86.13–129.19) ²¹	160.91 (128.73–193.09) ²⁵	
Diarrhea	38.55 (64.32–96.48) ²¹	60.18 (48.14–72.22) ²⁵	
Hypertension	80.4 (9.88–14.82) ²¹	233.72 (186.98–280.46) ²⁵	
Thrombocytopenia	3313.89 (2651.11–3976.67) ²¹	4646.71 (3717.37–5576.05) ²⁵	
Hand-foot syndrome	14.85 (11.88–17.82) ²¹	137.53 (110.02–165.04) ²⁵	
Total AEs cost of PK (grade \geq 3)	157.09 (125.67–188.51) ^b	261.46 (209.17–313.75) ^b	Gamma
Total AEs cost of standard (grade \geq 3)	527.81 (422.25–633.37) ^b	788.51 (630.81–946.21) ^b	Gamma
Utility			
Utility of PFS	0.73 (0.58–0.88) ²⁶		Beta
Utility of second-line treatment	0.66 (0.53–0.79) ²⁶		Beta
Utility of third-line treatment	0.55 (0.44–0.66) ²⁷		Beta
Disutility due to AEs (grades 1 and 2)	0.014 (0.008–0.02) ²⁴		Beta
Disutility due to AEs (grade \geq 3)	0.157 (0.11–0.204) ²⁴		Beta
Other			
Discount rate	5% (0–8%)		Fixed
AE, adverse event; BSC, best supportive care; PFS, progression-free survival; PK, pharmacokinetics; TDM, therapeutic drug monitoring. ^a The costs come from local charge. ^b The total cost is a weighted average of the cost per adverse event and the incidence per adverse event.			

1000 times, and the results were presented as a scatter plot of incremental cost effects. Probability parameters and utility values with values between 0 and 1 were set to beta distribution, and cost parameters with values greater than 0 and positively biased were set to gamma distribution. A cost-effectiveness acceptability curve was constructed to summarize the uncertainty of the evaluation under different WTP thresholds.

Results

Study characteristics

Among the 556 possibly relevant reports, 22 were proven to be eligible after duplicate removal and abstract screening. Subsequently, 17 studies were excluded (6 were conference abstracts, 6 were inappropriate interventions or comparisons, 2 were data duplication, and 3 had inconsistent

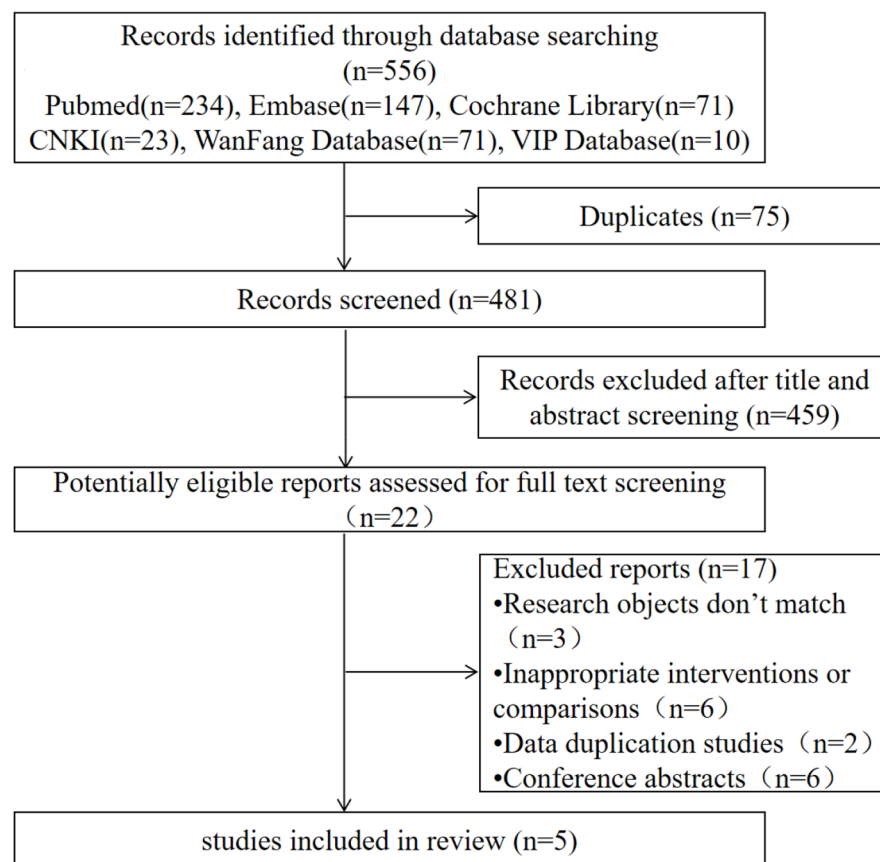


Figure 2. Flowchart of study selection.

research objects). Upon full-text screening, five studies^{9–13} were ultimately included in the systematic review, of which one was a phase II clinical trial⁹ and four were cohort studies.^{10–13} A total of 519 patients were included, 306 of whom were in the PK-guided arm and 213 were in the standard dose arm. The flowchart of study selection is shown in Figure 2, and the characteristics of these trials are summarized in Table 3.

Quality of included studies

The results of the quality assessment based on the Cochrane risk of bias tool for the included RCT are shown in Supplementary Table S2a. A major source of bias was its non-blind study design (open-label nature). The source of two other biases was unclear because of lack of data. The results of the quality assessment using NOS for the included nonrandomized studies are shown in Supplementary Table S2b. Only three studies received a score of 6 points or more (indicating high quality), and one cohort study received a score of 5 points due to insufficient article information (indicating low

quality). For comparability, all studies were scored 0 because of the lack of report on whether the intervention and control groups were matched according to specific factors. Given that the studies with a score of 6 or more were retrospective or prospective cohort, the number of patients included was relatively small, and complete outcome indicators were lacking. After comprehensive examination, the cost-effectiveness analysis was conducted using phase II clinical trial data.

Cost-effectiveness analysis

Base-case analysis. Model validation results showed that the OS and PFS generated by the model were close to those obtained in the clinical trials (Supplementary Figures S1–S4), indicating the consistency between the data from the fitting curve and the original data.

Table 4 shows the costs and health outcomes of two strategies obtained after running the model. The QALY of the patients in the PK-guided group increased by 0.83 compared with that in

Table 3. Summary of basic characteristics of studies.

Author(s) (Year)	Country	Study design	Disease type	1. Tumor response evaluation 2. Adverse events evaluation	Regimens	No. of Patients	Sunitinib concentration measurement	Dose adjustment	Outcome indicators
Bjarnason <i>et al.</i> ⁹	Canada	Phase 2 clinical trial	mRCC	1.RECIST v.1.1 2.NCI CTCAE v.3.0	Standard dose	147		50mg/day, 4/2	PFS, ORR, OS, toxicity
Noda <i>et al.</i> ¹⁰	Japan	Retrospective	mRCC	1.RECIST v.1.1 2.NCI CTCAE v.4.0	PK-guided dose Standard dose	117 8	HPLC	Based on sunitinib and SU012662 concentrations 50mg/day, 4/2	PFS, OS
Lankheet <i>et al.</i> ¹¹	Netherlands	Prospective	aRCC	1.RECIST v.1.1 2.NCI CTCAE v.4.0	PK-guided dose Standard dose	13 13	HPLC	The total concentration of sunitinib (sunitinib + SU12662) 100 ng/ml is the target concentration 37.5mg/day, once daily continuously	Toxicity
Bjarnason <i>et al.</i> ¹²	Canada	Retrospective	mRCC	1.RECIST v.1.1 2.NCI CTCAE v.4.0	PK-guided dose Standard dose	29 38	LC-MS/MS	TTL < 50 ng/ml is the target concentration, Sunitinib dose levels allowed were 12.5, 25, 37.5, 50, and 62.5 mg QD 50mg/day, 4/2	PFS, OS
Takasaki <i>et al.</i> ¹³	Japan	Prospective	mRCC	1.RECIST v.1.1 2.NCI CTCAE v.3.0	PK-guided dose Standard dose	134 7	HPLC	Based on sunitinib concentration to adjust dose; Dose adjustment methods are divided into the following four schemes: (1) 50 mg/day, 2/1; (2) 50 mg/day-7;(3) 37.5 mg/day-7;(4) 25 mg/day-7 50mg/day, 4/2	PFS, TTF, toxicity
<p>aRCC, advanced renal cell cancer; HPLC, high-performance liquid chromatography; LC-MS, liquid chromatography-mass spectrometry; mRCC, metastatic renal cell cancer; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events version; ORR, objective response rate; OS, overall survival; PFS, progression free survival; PK, pharmacokinetics; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumours; TTF, time to treatment failure; TTL, total trough level.</p>									

Table 4. Base-case results.

Strategy	Costs (US\$)	ΔCosts (US\$)	QALY	ΔQALY	ICER (US\$/QALY)	Dominance
China						
PK-guided	133,547.95	—	2.77	—	—	
Standard dose	151,376.73	17,828.78	1.94	-0.83	-21,594.83	Dominated
United States						
PK-guided	884,982.65	99,231.52	2.77	—	—	
Standard dose	984,214.16	—	1.94	-0.83	-120,192.60	Dominated

ICER, incremental cost-effectiveness ratio; PK, pharmacokinetics; QALY, quality-adjusted life years.

the standard dose group. The ICER for PK-guided dose *versus* standard dose was -21,594.83 US\$/QALY in China and -120,192.60 US\$/QALY in the United States. Therefore, PK-guided individualized dosing is cost-effective because of its low price and additional health outcomes.

Sensitivity analysis. One-way sensitivity analysis showed that the results were robust to parameter changes. Within the variation range of each parameter, the results had the highest sensitivity to the discount rate, followed by the cost of terminal care. However, the variation did not exceed the threshold, that is, the result cannot be reversed. For the United States, the results were also most sensitive to the discount rate, followed by the cost of sunitinib. Similarly, these parameters cannot reverse the results (Figure 3). For incremental cost-effectiveness, probabilistic sensitivity analysis showed that 100% of the scatter points were above the threshold line in China and the United States. This finding indicated that the economical results of the standard dose group were inferior to those of PK-guided group, and this result was reliable (Figure 4).

Discussion

Owing to the small number of included studies and the inconsistent quality of the articles, the intervention and control groups were not matched by propensity, and the resulting large heterogeneity prevented any formal meta-analysis. Therefore, the results used in the decision analysis model were based on the best relevant data of existing research without statistical synthesis. This study is the first to evaluate the cost-effectiveness of PK-guided sunitinib administration in untreated patients with mRCC. The PK-guided dose had lower costs and produced more QALYs than the

standard dose, suggesting the cost-effectiveness of the former. Sensitivity analysis was conducted on the major influencing factors to verify the stability of the model and the reliability of the advantage strategy. Given the variation in drug prices across different regions due to local affordability and market scheme, diverse health settings were considered in the economic evaluation for easy transferability among different regions. Given that the clinical data and utility values were obtained from foreign countries, the economics of the two strategies was analyzed from the perspective of Chinese and American health systems to reflect realistic results.

Although sunitinib has evidence-based clinical efficacy, its severe toxicity to certain patients has become an important issue in clinical decision-making for appropriate treatment. Considerable drug exposure may be one of the reasons for the serious toxicity of this medication.¹³ For patients of different body weights, genders, or ages, the recommended dose is 50 mg/day (dose reduction is only considered when serious AEs have occurred); hence, the PK variability has remarkably increased among individuals.²⁸ With the subsequent emergence of treatment-related AEs, maintaining the standard dosing regimen of sunitinib might be difficult. Therefore, other schedules have been proposed to improve the safety and increase the dose intensity of sunitinib. One alternative is sunitinib 50 mg/day with 2 weeks on treatment and 1 week off (schedule 2/1) and 37.5 mg/day on the continuous daily dosing (CDD) schedule. Based on the available evidence, the 2/1 schedule is relatively more effective and safer than the 4/2 schedule, and is feasible way to maintain drug level.^{29,30} Comparison of intermittent *versus* continuous dosing regimens revealed

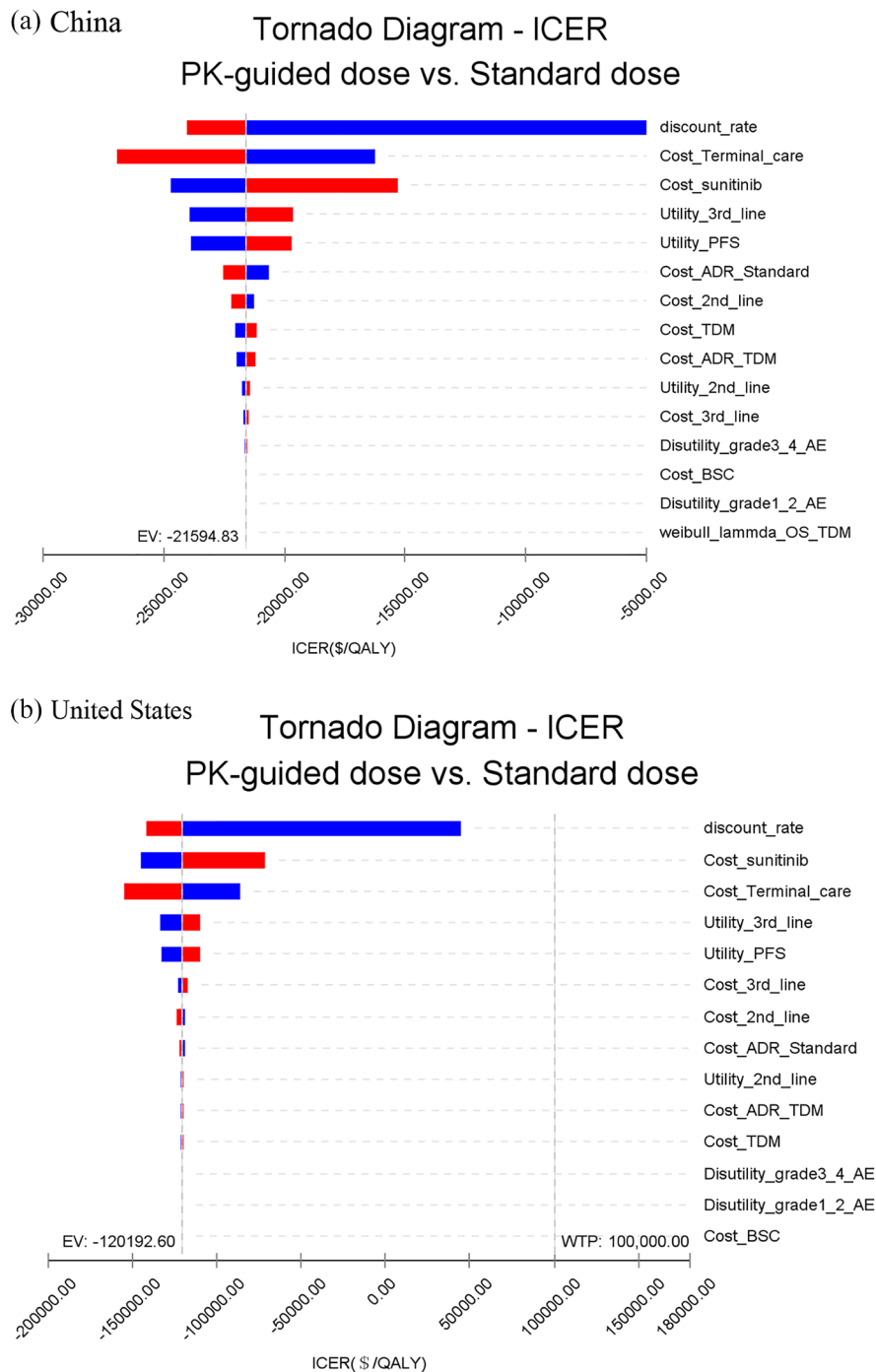


Figure 3. Tornado diagram: results of one-way deterministic sensitivity analysis.

that CDD does not have any advantage over 4/2 schedule in terms of the incidence or severity of AEs or patient-reported outcomes.¹⁸

Clinically, because the AEs risk from low-dose sunitinib is lower than that from high-dose sunitinib, many clinicians will choose to directly give low-dose

sunitinib to patients with mRCC to avoid the risk. This practice is actually not recommended. Clinicians are required to balance the clinical efficacy and the risk of toxicity and choose the appropriate treatment regimen for the patient, rather than reducing the risk of AEs only by reducing the dose. Admittedly, 2/1 schedule is safer and more effective

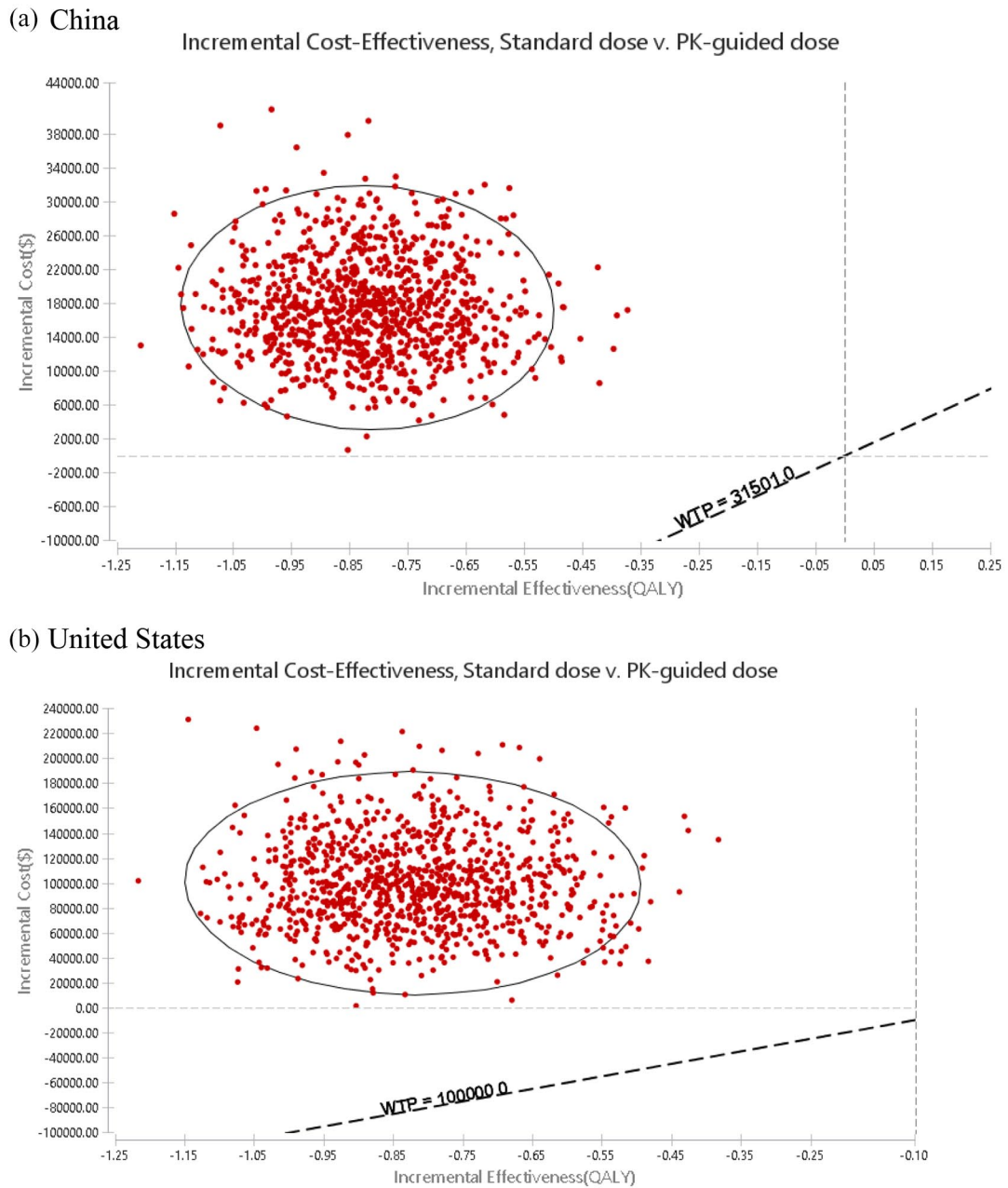


Figure 4. Incremental cost-effective scatter plot of standard group versus PK-guided group.

than 4/2 schedule and more convenient than TDM, but unfortunately it may not be suitable for all patients. Regardless of the schedule, good treatment results and few adverse reactions are not guaranteed for all patients. Therefore, it is important to adjust the drug concentration appropriately according to the actual situation of the patient, rather than a unified schedule. In addition, TDM could also be helpful in unique populations, such as in age or weight extremes (children, elderly, patients with limb

amputation, or obese patients), or rare ethnic/genetic groups of patients.

This study has limitations. First, the phase II clinical trial data used in the cost-effectiveness analysis was a single-arm study. The control group was based on patients with similar qualification standards who received standard dose, resulting in differences in patients' baseline characteristics and follow-up personnel. This phenomenon would have a certain

impact on the reliability of current results. Therefore, a prospective randomized clinical trial is needed to finally determine the value of PK-guided dose. Second, the clinical trial data used in the model were obtained from a foreign phase II clinical trial, and the utility value was derived from the EQ-5D (EuroQol five-dimension questionnaire) scale score for Dutch patients with mRCC. Therefore, the current findings may not reflect Chinese data. However, sensitivity analysis showed that these parameters have minimal impact on the cost-effectiveness of treatment strategies. Third, the actual dose intensity of drugs after adopting PK guidance was not provided in the evaluation of drug cost, leading to the possibility of dose downward or upward adjustment. Hence, the drug cost of PK group was not accurately estimated. Although the current hypothesis was consistent with the standard dose with minimal deviations, the results cannot be reversed. Fourth, various phase 3 studies showed that the actual median dose of sunitinib ranges 30–46 mg/day for patients using a fixed dose of 50 mg/day. Given that this median dose is difficult to accurately quantify, the 50 mg dose was still used in the model. However, setting the cost of sunitinib at ± 50 to reduce the difference caused by hypothesis would consequently decrease its impact on the actual results. Fifth, the cost of grade 1/2 AEs was excluded because of lack of evidence indicating the notable differences between PK-guided and standard doses. In addition, cost data sources were currently unavailable. To date, many large hospitals in China have not yet launched the TDM of sunitinib. Despite these limitations, the results reflect the general clinical conditions of Chinese patients with mRCC and provide important reference for Chinese decision-makers.

Conclusion

From the perspective of China and US health systems, the PK-guided treatment of sunitinib may be a safe, effective, and economical intervention for patients with mRCC.

Author contributions

Tingting Chen: Data curation; Formal analysis; Methodology; Software; Writing – original draft.

Jiahe Chen: Data curation; Methodology; Software; Writing – review & editing.

Chaoxin Chen: Formal analysis; Methodology; Software; Writing – review & editing.

Jianming Guo: Conceptualization; Methodology; Software; Validation.

Xin He: Investigation; Methodology; Validation.

Song Zheng: Investigation; Methodology; Validation.

Maobai Liu: Funding acquisition; Investigation; Project administration.

Bin Zheng: Conceptualization; Funding acquisition; Investigation; Writing – review & editing.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by Science and Technology Department of Fujian Province (grant number: 2020R0052) and Joint Funds for the innovation of science and Technology, Fujian province (Grant number: 2018Y9037).

Ethics statement

This study was based on a literature review and modeling techniques; this study did not require approval by an institutional research ethics board.

Supplemental material

Supplemental material for this article is available online.

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